Annals of Clinical and Analytical Medicine
Original Research

Anti-inflammatory therapy in patients with severe COVID-19 pneumonia: A single-center observational study

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Abstract
Aim: In our study, the effects of methylprednisolone and anakinra drugs in the treatment of hyperinflammation in severe COVID-19 patients were investigated.
Material and Methods: In this single-center retrospective study, severe COVID-19 patients followed up with signs of hyperinflammation were examined. The patients were examined in the Sequential Treatment Group receiving high-dose methylprednisolone followed by Anakinra, and the concomitant treatment group receiving both at the same time. Inflammatory parameters, imaging findings, and way of leaving the intensive care unit of the patients were compared.
Results: A total of 87 patients were included in the present study. In both treatment groups, an increase in lymphocyte levels and a decrease in CRP, lactate dehydrogenase (LDH) and ferritin levels were detected at the end of treatment values compared to the initial treatment values. ($p<0.001$ and $p<0.001$). Also, LDH values after the treatment were significantly lower in the concomitant treatment group than in the sequential treatment group ($p=0.049$). In the present study, 53 of the patients were discharged with good recovery and 34 died. The mortality rate was 31% in the concomitant treatment group and 43% in the sequential treatment group. In terms of mortality, numerical findings in favor of the concurrent treatment group were determined.
Discussion: In addition to the studies in the literature, it was found that the concomitant use of Methylprednisolone and Anakinra can be an effective treatment option that reduces mortality and improves inflammatory parameters.

Keywords
Anakinra, Methylprednisolone, Mortality

DOI: 10.4328/ACAM.21185 Received: 2022-04-13 Accepted: 2022-05-31 Published Online: 2022-06-24 Printed: 2022-09-01 Ann Clin Anal Med 2022;13(9):993-998
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Introduction

COVID-19, caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), although mostly asymptomatic or mildly symptomatic disease, it may also require hospital treatment in 10-15% of cases with moderate to severe disease symptoms. Also, 3-5% of the cases are severe enough to require hospitalization in the Intensive Care Units [1,2].

The clinical manifestations of COVID-19 can be described in three phases [3]. High fever and pneumonia-like symptoms may occur following flu-like symptoms. While direct tissue damage by SARS-CoV-2 infection is seen in the lungs, an exaggerated host immune response triggered by this infection has also been demonstrated. Proinflammatory cytokines play an important role in the pathogenesis of COVID-19. A small proportion of COVID-19 patients proceed to stage three, where systemic hyperinflammation develops, in which there is an increase in cytokine storm markers such as C-reactive protein, ferritin, lactate dehydrogenase, and D-dimer and a significant decrease in lymphocytes. Acute Respiratory Distress Syndrome (ARDS) or cytokine storm, and cardiac and renal damage are the leading causes of mortality, especially for patients who have advanced age and comorbidities [1,4-6].

After the concept of cytokine storm was defined in COVID-19 patients, treatments to suppress proinflammatory cytokines such as interleukin 1 (IL-1) and interleukin 6 (IL-6) came to the fore [7]. The IL-1-receptor antagonist anakinra, which has a half-life of approximately 3-4 hours and is used in the treatment of rheumatological diseases, is one of the cytokine blocking agents used for the treatment of COVID-19 [8]. Along with ongoing randomized clinical trials, the results of studies conducted in more than one center are promising. Anakinra's short half-life makes it suitable for use in critically ill patients, as its effect can be stopped quickly in case of possible secondary infections [9-11].

Corticosteroid therapy, on the other hand, is used in the treatment management of cytokine storm [8]. In prospective, randomized clinical trials in critically ill patients with COVID-19, corticosteroid use significantly reduced 28-day mortality compared to patients given placebo or standard care [12].

In the present study, the purpose was to investigate the effects of concurrent or successive use of Anakinra and methylprednisolone (anti-IL-1+MPD) on biochemical parameters, mortality, and oxygen need in severe COVID-19 patients.

Material and Methods

The present study is a single-center retrospective study that included the data of patients followed in the COVID-19 Intensive Care Unit of our hospital between October and December 2020. Ethical approval for the study was obtained from the Non-Interventional Ethics Committee of Mustafa Kemal University with the date 06/05/2021 and the decision number 04.

Inclusion Criteria

The patients who were over 18 years of age and had SARS-CoV-2 infection proven by Polymerase Chain Reaction were included in the study. Those who responded to standard treatment, patients with negative SARS-CoV-2 PCR test, patients without Thorax Computed Tomography results, and patients with deficiencies in laboratory tests on the first and final day of the treatment were excluded from the study.

The definition and staging of ARDS were made in accordance with national COVID-19 guidelines.

Thorax Computed Tomography evaluation was made by the radiologists of the hospital. Classification was made in the reporting as "mild-moderate and severe involvement" according to the involvement rates of the lungs. Involvement of less than 25% of both lungs was considered mild, 25-50% of involvement was considered moderate, and involvement of more than 50% was considered severe pneumonia.

The criteria for patients who were thought to develop macrophage activation syndrome, despite treatment, were T.C. Ministry of Health General Directorate of Public Health COVID-19 anticytokine-anti-inflammatory treatments, which were determined in accordance with the coagulopathy management guidelines.

Treatment Protocol

Every patient who was hospitalized due to the diagnosis of COVID-19 was treated in line with the T.C. Ministry of Health General Directorate of Public Health Adult Patient Treatment Guideline; Favipiravir, low molecular weight heparin and proton pump inhibitor treatment were applied as standard protocol. High-dose corticosteroid and anti-cytokine treatments were applied for patients who were considered to develop macrophage activation syndrome despite treatment.

As pulse steroid treatment, in line with the COVID-19 Anticytokine-Anti-Inflammatory Treatment and Coagulopathy Management Guideline of the Ministry of Health, General Directorate of Public Health, 250 mg/day Methyl Prednisolone was administered for 3 days to patients with high oxygen demand due to respiratory distress and considered to have a non-infectious hyper-inflammatory clinical manifestation. In line with the same guideline, Anakinra treatment was subcutaneously administered in 4 equal doses with a maximum of 800 mg/day. According to the decrease in the daily oxygen need of the patient, 600 mg/day and 400 mg/day doses were given with 3-day follow-up periods. Anakinra treatment was administered for a maximum of 10 days.

If Anakinra was found in the hospital pharmacy, both concurrent treatments were initiated with MPD to start the treatment faster in the study, and if the drug was not available in the hospital pharmacy, Anakinra was administered first after the MPD. As a result of these compulsory treatments, the patients were divided into two groups as those who received successive treatment and those who received concurrent treatment.

Statistical Analysis

Continuous variables were presented as a mean ± standard deviation, median (min-max); and categorical data were expressed as numbers and percentages. Normality analyzes of the continuous variables were made with the Kolmogorov-Smirnov Goodness of Fit Test. T-Test was used for independent groups in the comparisons of the data with normal distribution, and the Mann-Whitney U-Test was used for those that did not. The comparisons of the categorical data were made with the Chi-Square Test. T-Test for Dependent Groups was used to compare the data with normal distribution in intra-group analyses, and Wilcoxon Ordered Signs Test was used for those that did not. The analyses were made with the IBM SPSS

(Statistics Package Program for Social Sciences) version 22.0 (IBM Corporation, Armonk, NY, USA). Statistical significance level was taken as p<0.05.

Results

The study included 87 PCR-positive patients, 59 of whom were male, who were followed up in the COVID-19 Intensive Care Unit of our hospital between October and December 2020. The mean age of the patients was 63.24±11.85 years. In both treatment groups, patients had similar rates of comorbid diseases (diabetes mellitus, hypertension, coronary artery disease, etc.). Although it was not statistically significant, it was observed that the difference was numerically significant in favor of the group receiving simultaneous treatment.

The lymphocyte levels were found to be statistically and significantly higher in both groups after the treatment when compared to before (p<0.001 and p=0.008, respectively). The intra- and intergroup comparison of the whole blood parameters of the patients is given in Table 1. Also, in the results of biochemistry tests, there were no significant differences between the groups in terms of the urea, creatinine, AST, ALT, Procalcitonin (PCT), CRP, D-Dimer, and ferritin values on the first day of the treatment and at the end of the treatment (p>0.05), and the LDH values after the treatment were significantly lower in the concurrent treatment group than in the successive treatment group (p=0.049).

In the intragroup evaluations of both groups, the CRP, LDH, and ferritin values were statistically and significantly decreased after the treatment when compared to the pre-treatment period (p<0.001 and p<0.001, respectively). In the evaluation of the biochemical test results of the patients, a significant improvement compared to the initial values was more pronounced in the concomitant treatment group.

Also, when the patients were compared according to the way they left the Intensive Care Unit in the present study, 53 patients were discharged and 34 patients died. Statistically significant differences were detected in the discharged patient group in terms of ARDS and lung involvement in Thorax Tomography of these patients (Table 2)

In the comparisons made according to the discharge status of the patients from the hospital, it was found that SO2 and lymphocyte levels on the first day of the treatment and at the end of the treatment were significantly lower in the patients who died when compared to the patients who were discharged (p=0.019, p<0.001, p=0.002, and p=0.001, respectively). The LDH, CRP, and ferritin levels were significantly higher in those who died (p<0.001, p<0.001, p=0.021, p<0.001, p=0.014 and p<0.001, respectively).

Table 1. Intra- and intergroup comparison of whole blood parameters, routine blood parameters, and some inflammatory markers

	Anakinra (Successive treatment) (n=55)	Anakinra+MPD (Concurrent treatment) (n=32)	p
WBC 1. day (Mean±SD) (/µL)	12583,45±4492,88	12091,06±5220,92	0.644*
WBC final day (Mean±SD) (/µL)	10880,39±6400,58	10461,51±7035,35	0.780*
	p=0.128**	p=0.350**	
Neutrophil 1. day [median (min-max)] (/µL)	9700 (4500-22094)	9650 (2500-21670)	0.249***
Neutrophil final day [median (min-max)] (/µL)	9460 (1788-42900)	9600 (3950-23200)	0.600***
	p=0.596****	p=0.914****	
Lymphocyte 1. day [median (min-max)] (/µL)	790 (280-3600)	800 (230-3000)	0.937***
Lymphocyte final day [median (min-max)] (/µL)	1215 (180-7000)	1480 (110-8600)	0.661***
	p<0.001****	p=0.008****	
CRP 1. day [median (min-max)](mg/L)	64 (2,6-236)	64 (2,8-218)	0.644***
CRP final day [median (min-max)](mg/L)	12,7 (0,9-307)	9,9 (0,6-345)	0.374***
	p<0.001****	p=0.018****	
LDH 1. day [median (min-max)] (IU/L)	491 (243-1500)	475,5 (305-930)	0.223***
LDH final day [median (min-max)] (IU/L)	392 (4,7-4316)	316,5 (9,8-3927)	0.049***
	p<0.001****	p=0.019****	
D-Dimer 1. day [median (min-max)](µg/mL)	0,76 (0,08-154)	0,54 (0,05-8,28)	0.111***
D-Dimer final day [median (min-max)] (µg/mL)	0,70 (0,12-414)	0,49 (0,08-9,6)	0.446***
	p=0.826****	p=0.820****	
Ferritin 1. day [median (min-max)] (µg/L)	812,5 (64-2000)	669,2 (5-2000)	0.816***
Ferritin final day [median (min-max)] (µg/L)	615 (41-2000)	614,2 (3,4-2000)	0.655***
	p=0.037****	p=0.037****	
Oxygen treatments (n, %)			
Nasal	6 (10,9)	3 (9,4)	0.712****
Reservoir mask	33 (60,0)	23 (71,9)	
NIMV	10 (18,2)	4 (12,5)	
MV	6 (10,9)	2 (6,3)	
Final status (n, %)			
Discharge	31 (56,4)	22 (69,8)	0.519****
Mortality	24 (43,6)	10 (31,3)	

* T-Test in Independent Groups ** T-Test in Dependent Groups, *** Mann-Whitney U Test **** Wilcoxon Ranked Signs Test, ***** Chi-Square Test, WBC: White Blood Cell, CRP: C-Reactive Protein, LDH: Lactate Dehydrogenase

It was observed in intragroup evaluations that SO2 and lymphocyte values increased at significant levels, and LDH, CRP, and ferritin values decreased at significant levels at the end of the treatment in patients who were discharged. However, no significant differences were detected in the patients who lost their lives after the treatment when compared to the initiation of treatment (p>0.05) (Table 3).

Table 2. Comparison of some demographic and clinical characteristics according to the final status of the patients

	Discharge (n=53)	Mortality (n=34)	
Age (Mean±SD)	60,86±10,99	67,20±12,61	0.015*
Treatment duration [median (min-max)]	10 (5-40)	12 (2-30)	0.890**
ARDS (n,%)			
Mild	13 (24,5)	2 (5,9)	
Moderate	31 (58,5)	10 (29,4)	<0.001***
Severe	9 (17,0)	22 (64,7)	
Thoracic Tomography (n,%)			.
Moderate	32 (64,0)	10 (29,4)	0.005***
Severe	21 (39,6)	24 (70,6)	
Oxygen treatments (n,%)			.
Nasal	7 (13,2)	2 (5,9)	
Reservoir mask	41 (77,4)	15 (44,1)	<0.001***
NIMV	4 (7,5)	10 (29,4)	
MV	1 (1,9)	7 (20,6)	
Treatment agent (n,%)			.
Anakinra	31 (58,5)	25 (70,6)	0.254***
Anakinra + MPD	22 (41,5)	10 (29,4)	

* T-test, ** Mann-Whitney U test, *** Chi-Square Test, ARDS: Acute Respiratory Distress Syndrome NIMV: Noninvasive Mechanic Ventilation MV: Mechanic Ventilation

Table 3. Intra- and intergroup comparison of SO2 levels and some inflammatory markers

	Discharge (n=53)	Mortality (n=34)	p
SO2 1. day [median (min-max)](%)	90 (80-99)	88 (72-97)	0.019 *
SO2 final day [median (min-max)] (%)	95 (85-99)	90 (75-99)	<0.00 *
	p<0.001**	p=0.113 **	
LDH 1. day [median (min-max)] (IU/L)	446 (243-1147)	640,5 (245-1500)	<0.001*
LDH final day [median (min-max)] (IU/L)	319 (4,7-1060)	590 (9,8-4316)	<0.001*
	p<0.001**	p=0.458 **	
CRP 1. day [median (min-max)] (mg/L)	41,8 (2,6-176,3)	93,9 (2,8-236)	0.021*
CRP final day [median (min-max)] (mg/L)	5 (0,6-215)	39 (0,9-345)	<0.001*
	p<0.001 **	p=0.550 **	
Ferritin 1. day [median (min-max)] (µg/L)	629 (5-2000)	970 (99,4-2000)	0.014*
Ferritin final day [median (min-max)] (µg/L)	418 (3,4-2000)	1237 (70,6-2000)	<0.001*
	p<0.001 **	p=0.124 **	
Lymphocyte 1. day [median (min-max)] (/µL)	860 (230-3000)	570 (280-3600)	0.002 *
Lymphocyte final day [median (min-max)] (/µL)	1484 (0,46-36400)	542 (0,11-7000)	0.001*
	p=0.004 **	p=0.110 **	

* Mann-Whitney U Test, ** Wilcoxon-Ranked Signs Test, SO2: Saturation, CRP: C-Reactive Protein, LDH: Lactate Dehydrogenase

Discussion

The effects of concurrent or successive use of Anakinra and MPD treatment on clinical improvement and mortality were investigated in the study. Improvement was detected in oxygenation of the patients and improvement was detected in inflammatory parameters with the concurrent initiation of anti-inflammatory and anti-cytokine treatment. In our study, lymphocyte count increased with treatment, while LDH, CRP and ferritin values decreased.

There was no difference between the two groups in our study in terms of demographic characteristics and duration of treatment. Demographic data, age range, percentage of gender and similar rates of comorbid diseases were found compatible with the literature data [10,14-16]. Although no statistical differences were detected in terms of discharge rates in patients who received concurrent treatment, it is numerically promising that 22 (70%) out of 32 patients who received this treatment were discharged.

A total of 53 (60.9%) of the 87 patients who participated in the study were discharged, and 10 out of the 34 patients who lost their lives received concurrent treatment, while 24 received successive treatment. Studies in the literature mostly compared the patient group administered with anti-inflammatory/anti-cytokine treatment with patients who received standard treatment. A low 28-day mortality and invasive Mechanical Ventilation (MV) need rates were reported in the Randomized Evaluation of the COVID-19 Treatment (RECOVERY) Study, which had the largest number of patients among these studies [17]. Similarly, in other studies that were conducted with Methylprednisolone (MPD) in the USA and the Netherlands, Mechanical Ventilation and mortality rates were lower in the treatment groups [16,18-20]. In another study, in which 65 patients received Anakinra+MPD and 55 patients received standard treatment, mortality and MV rates were higher in patients who received standard treatment [14]. Patients were given MPD for three days first, followed by Tocilizumab and Anakinra treatment, which was administered to patients with worsening oxygenation in a study that was conducted in Spain. No deaths occurred in the group that received Anakinra as the last treatment in this study. The authors reported that Anakinra can be used instead of Tocilizumab in patients with severe COVID-19-related hyperinflammation if corticosteroid treatment fails with the current findings [21]. In the comparison of two different treatment groups in the present study, similar to the decreased mortality rates when compared to standard treatment in the studies in the literature, it was found that the concurrent treatment had positive effects on mortality. The low number of patients and the limited retrospective data are considered to have contributed to the lack of statistically significant rates in our study.

In the present study, there were 16 patients in the successive treatment group who received Noninvasive Mechanical Ventilation (NIMV) and MV support, and 6 patients in the concurrent treatment group; and 12 of the 16 patients who received support and 4 of 6 patients died. Mortality rates were found to be significantly higher in both treatment groups. However, Anakinra treatment that was administered to the

patients who received NIMV support in Italy showed significant decreases in both 28-day and 90-day mortality rates [22]. In this study, the success of Anakinra treatment was shown even in patients who received NIMV support. However, we believe that the moderate-to-severe ARDS involvement in the patients who participated in the present study might have effects on our high mortality rates.

The number of lymphocytes was increased at statistically significant levels when compared to the first day of the treatment in both treatment groups. Also, ferritin, LDH and CRP values decreased with the treatment. A total of 65 patients were treated with Anakinra + Methylprednisolone in the study that was conducted by Bozzi et al. in Italy. It was found that the CRP values of the patients in the treatment group decreased rapidly throughout the treatment period [14]. In a prospective study that evaluated 21 patients followed up for 10 days before the treatment and 10 days after the start of treatment, a decrease was detected in CRP and ferritin values in patients who received Anakinra [16]. In a similar study conducted by Huet et al., a rapid decrease was detected in the CRP values of the patients in the treatment group on the 4th day of the treatment [10]. As a result of the decreased hypoxia levels with treatment, an improvement was detected in the end-of-treatment values of the parameters, which indicated tissue damage. In the results of our study, decreases were detected in the ferritin values that increased as an acute phase reactant, increased LDH levels after tissue hypoxia, and in the CRP values that increased with cytokine release after the anti-inflammatory and anti-cytokine treatment. Increased lymphocyte values were detected with these treatments applied to patients with lymphopenia in the course of COVID-19.

When the evaluation was made according to the discharge and mortality status of the patients, as expected, it was found that the number of patients with severe ARDS, severe involvement on tomography, and those who needed NIMV and MV support was higher among those who died. When compared to the first day of treatment, a decrease in LDH, CRP and ferritin, and an increase in lymphocyte and SO2 values were detected at the end of the treatment in the discharged patient group. According to the ROC analysis results, the sensitivity in predicting mortality over 875 µg/L for ferritin was found to be 63% and the specificity was 68%. An increase in ferritin value can be a good marker for predicting mortality and macrophage activation syndrome [9]. An increase in ferritin value without clinical worsening may help initiation of immunomodulatory treatment early to prevent cytokine storm syndrome.

There were some limitations in the present study. Firstly, the fact that it had a retrospective and single-center design affected the generalizability of the results. Secondly, the superiority of Anakinra and methylprednisolone alone over the standard treatment modality was not investigated because the patients were not compared with the group receiving standard treatment in the study. Its strengths were that mostly Anakinra and/or methylprednisolone treatment was compared with patients receiving standard treatment in the literature. The number of studies similar to the design of the present study is limited. We believe that we have contributed to the literature with positive results regarding the concurrent use of Anakinra and MPD.

Conclusion

In conclusion, concurrent treatment with Anakinra and MPD may become a safe and effective treatment option in decreasing the oxygen demand and control SARS-CoV-2-induced inflammation in COVID-19 patients with hyperinflammation and respiratory failure. In this respect, it is necessary to conduct studies with a larger number of cases and with longer follow-up durations. Prospective studies can be conducted to evaluate the effectiveness of targeted therapy by measuring interleukin levels.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: *None*

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article:
Gülnur Kul, Gürkan Değirmencioğlu. *Anti-inflammatory therapy in patients with severe COVID-19 pneumonia: A single-center observational study. Ann Clin Anal Med 2022;13(9):993-998*